

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-16294	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2004/039763	International filing date (day/month/year) 13/12/2004	(Earliest) Priority Date (day/month/year) 23/12/2003
Applicant  ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

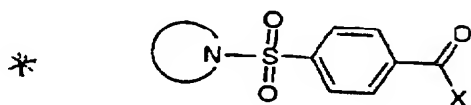
☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Novel compounds of structural formula (I)<sup>\*</sup> are disclosed. As modulators of the Cannabinoid-1 (CB1) receptor, these compounds are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. As such, compounds of the present invention are useful as in the treatment, prevention and suppression of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders (e.g., multiple sclerosis, Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis), cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, particularly to opiates, alcohol, and nicotine. The compounds are also useful for the treatment of obesity or eating disorders associated with excessive food intake and complications associated therewith.



Formula I

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/039763

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/08 C07D209/10 C07D209/42 C07D231/56 C07D471/04  
C07D401/04 C07D401/12 C07D403/12 C07D403/04 C07D417/04  
A61K31/404 A61K31/407 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	✓ WO 96/25397 A (MERCK FROSST CANADA INC; GALLANT, MICHEL; GAREAU, YVES; GUAY, DANIEL;) 22 August 1996 (1996-08-22) cited in the application examples	1-44
A	✓ WO 03/027076 A (SOLVAY PHARMACEUTICALS B.V; KRUSE, CORNELIS, G; LANGE, JOSEPHUS, H.M;) 3 April 2003 (2003-04-03) cited in the application examples	1-44
E	✓ EP 1 506 960 A (NATIONAL HEALTH RESEARCH INSTITUTES) 16 February 2005 (2005-02-16) examples 7,14	40
A	✓ US 2002/119972 A1 (LEFOTHERIS KATERINA ET AL) 29 August 2002 (2002-08-29) examples	1-44

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

7 April 2005

Date of mailing of the international search report

15/04/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
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Authorized officer

Menegaki, F

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2004/039763

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 30-33, 38, 39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/039763

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9625397	A	22-08-1996	US 5532237 A	02-07-1996
			AU 703913 B2	01-04-1999
			AU 4616696 A	04-09-1996
			CA 2211836 A1	22-08-1996
			WO 9625397 A1	22-08-1996
			EP 0809630 A1	03-12-1997
			JP 3033076 B2	17-04-2000
			JP 10508870 T	02-09-1998
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WO 03027076	A	03-04-2003	BR 0212481 A	24-08-2004
			CA 2457444 A1	03-04-2003
			WO 03027076 A2	03-04-2003
			EP 1438296 A2	21-07-2004
			HR 20040185 A2	31-08-2004
			HU 0402150 A2	28-02-2005
			JP 2005504805 T	17-02-2005
			US 2004235854 A1	25-11-2004
			US 2005054679 A1	10-03-2005
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EP 1506960	A	16-02-2005	EP 1506960 A1	16-02-2005
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US 2002119972	A1	29-08-2002	AU 3495801 A	20-08-2001
			CA 2399791 A1	16-08-2001
			EP 1254115 A2	06-11-2002
			JP 2004502642 T	29-01-2004
			WO 0158869 A2	16-08-2001
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

816294

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

23 Oct 2005

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION

See paragraph 2 below

International application No.  
PCTUS2004/039763

International filing date (day/month/year)  
13.12.2004

Priority date (day/month/year)  
23.12.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D209/08, C07D209/10, C07D209/42, C07D231/56, C07D471/04, C07D401/04, C07D401/12, C07D403/12,

Applicant  
ELI LILLY AND COMPANY

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Menegaki, F

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 30-33, 38, 39

because:

- ☒ the said international application, or the said claims Nos. 30-33, 38, 39 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details



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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-44
	No: Claims	
Inventive step (IS)	Yes: Claims	1-44
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-29, 34-37, 40-44
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

**see form 210**

(III)

Claims 30-33, 38, 39 are directed to a method of treatment of the human/animal body and therefore no preliminary examination is required (Rule 67.1(iv) PCT).

Moreover, it is noted by the IPEA that for the assessment of Claims 30-33, 38, 39 on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, e.g., does not recognize the subject-matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

(V)

Having regard to the International Search Report as well as the prior art cited by the Applicant in the description documents

D1: WO 96/25397 A (MERCK FROSST CANADA INC; GALLANT, MICHEL; GAREAU, YVES; GUAY, DANIEL;) 22 August 1996 (1996-08-22)

D2: WO 03/027076 A (SOLVAY PHARMACEUTICALS B.V; KRUSE, CORNELIS, G; LANGE, JOSEPHUS, H.M;) 3 April 2003 (2003-04-03)

D3: US 2002/119972 A1 (LEFETHERIS KATERINA ET AL) 29 August 2002 (2002-08-29)

disclose structurally different cannabinoid receptor modulators differing from the present compounds of formula (I).

The disclaimer in Claim 1 excludes three separate compounds falling under the scope of Formula (I), which are not known to possess similar activity.

Moreover, document

D4: EP-A-1 506 960 (NATIONAL HEALTH RESEARCH INSTITUTES) 16 February 2005 (2005-02-16), in particular Ex.7 and 14 therein differ from the present intermediates of formula (IIa) in Claim 40.

The requirements of Art.33(2) PCT appear to be fulfilled.

The problem to be solved appears to be the provision of novel CB-1R modulators of present formula (I), which were not structurally obvious from the prior art disclosure in (D1) to (D3).

The compounds excluded through the disclaimer are separate compounds not known to possess similar activity.

Therefore, an inventive step can be acknowledged *per se* on the basis of the test Example data on p.172, l.18-19 of the description, provided that all claimed compounds possess the desired CB-1R modulating activity.

The requirements of Art.33(3) PCT appear to be fulfilled.

Nevertheless, in this connection reference is made to the broad variation of the substituent groups in formula (I), compared with restricted activity data, which obviously cannot apply to all compounds, in view of the agonistic as well as antagonistic properties comprised in the term "modulating activity". The Applicant has not specified certain substituents' definitions as "(cyclo-)alkyl(-oxy/-amino); aryl; acyl; heterocyclyl" appearing in the definition of  $R^1(b),(c),(g)$ ;  $R^2(a)$ ;  $R^3(b),(c)$ .